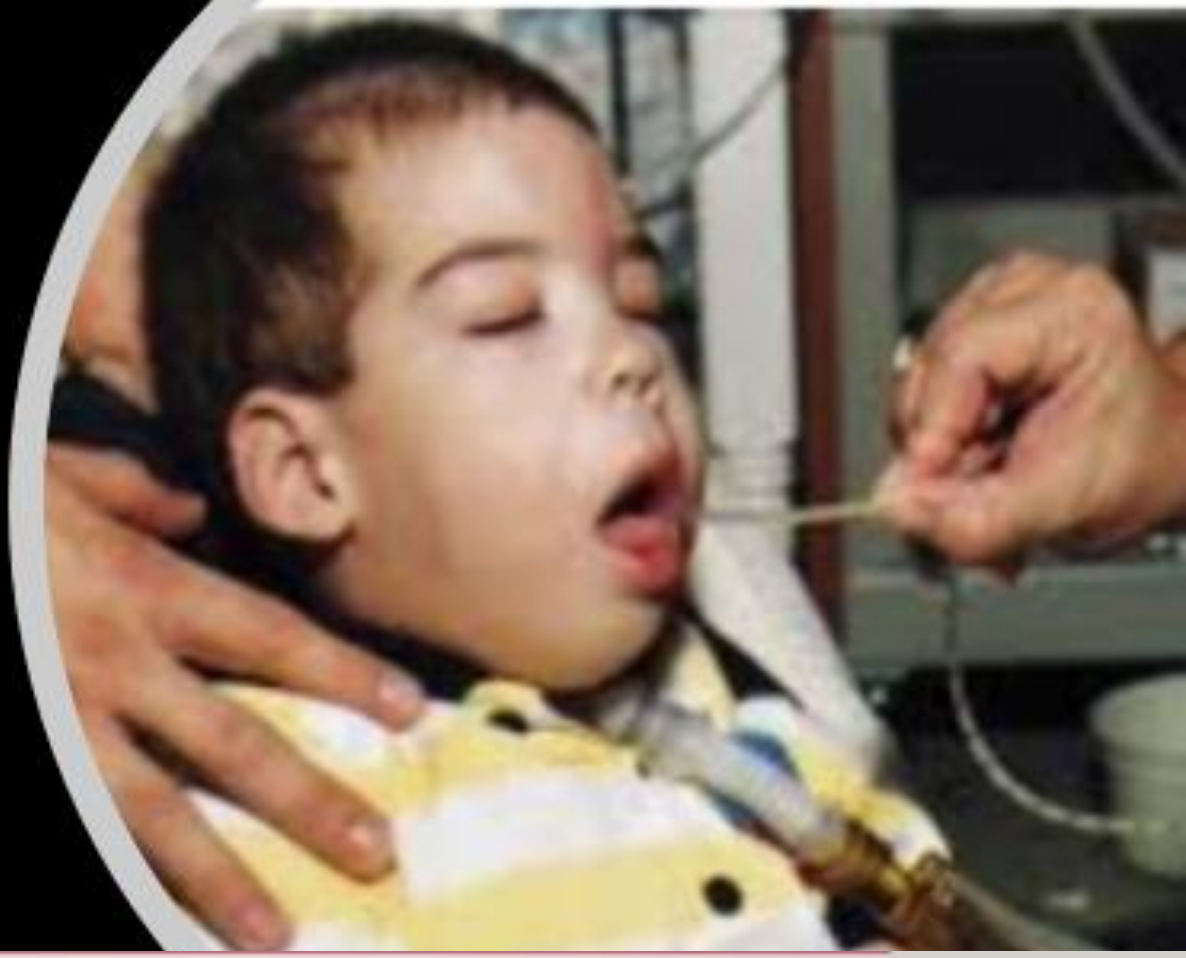
Respiratory Problems in Children with Neuromuscular Disorders



INAUGURAL PAEDIATRIC RESPIRATORY AND SLEEP MEDICINE SYMPOSIUM

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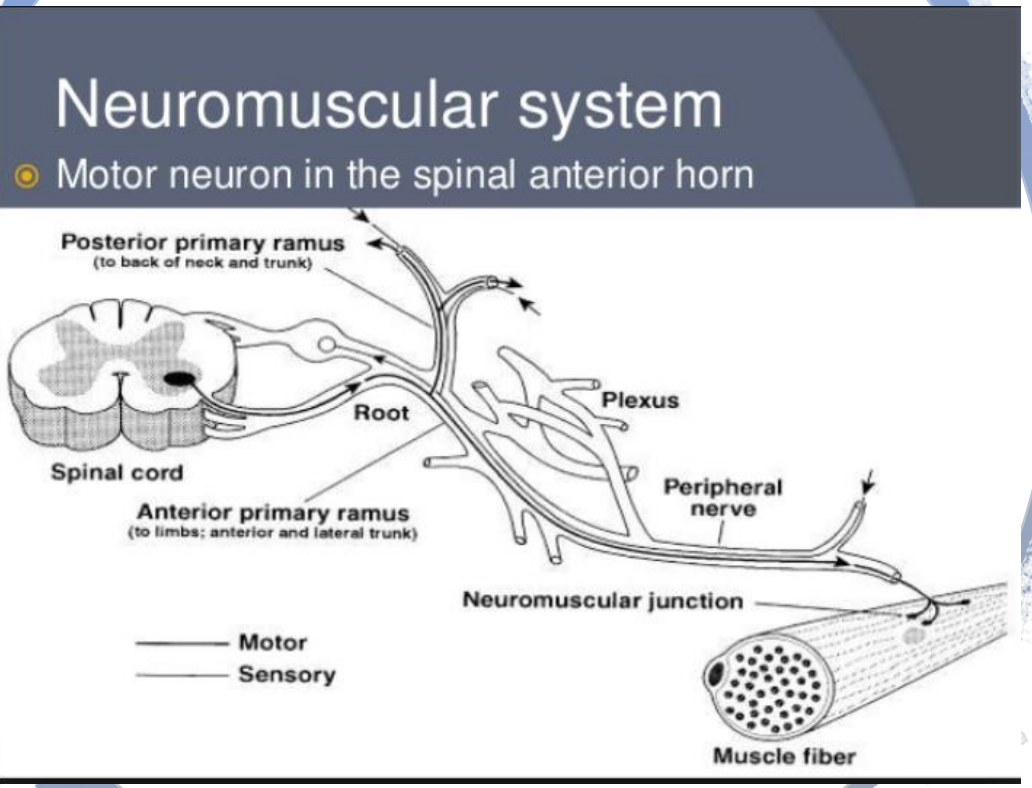


Neuromuscular disorders

Relatively common: 1 in 3000

Majority are genetic

Majority become apparent in childhood

SPINAL MUSCULAR ATROPHY - OVERVIEW

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease.It is caused by mutations in the survival motor neuron 1 (SMN1) gene. The disease is classified on the basis of age of onset and clinical course.

SMA type 0 (prenatal SMA)
The most severe form. Children usually succumb to the disease before the age of 6 months.

SMA type 2 (chronic infantile SMA)
Serious muscle weakness (assisted sitting and walking). Symptoms usually appear between 7-18 months of age.

SMA type 1 (Werdnig-Hoffman disease)
Symptoms appear within the first few months of life. Children rarely survive passed their 2nd birthday.

SMA type 4 (adult onset SMA)
Not a life-threatening condition. Symptoms appear in adulthood.

SMA type 3 (Kugelberg Welander disease)
Children are able to stand and walk, but worsen with time. Symptoms usually appear after 18 months of age.

Finkel type SMA
Also an adult onset disease, it is caused by mutations in another gene called VAPB.

SMARD1 (Distal SMA)
Clinically and genetically distinct and uncommon form of SMA.

SMA NEWS TODAY

www.smanewstoday.com

SPINAL MUSCULAR ATROPHY

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
SMA					
Type 1	All by 2 years	Marked	All	Rapid	All require full-time respiratory support
Type 2	~40% in childhood	Early	~25% in first 5 years	Slow	
Type 3	Rare in childhood	Rare in childhood	Rare in childhood	Slow	
SMA with respiratory distress type 1	All by 6 months	Marked	All	Rapid in first year, then slows.	All require full-time respiratory support

DMD/ LGMD/ FSHMD

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
DMD/severe childhood onset limb-girdle muscular dystrophy	After loss of ambulation	After loss of ambulation	Late		Cardiomyopathy usually occurs after respiratory problems but may precede them
Facioscapulohumeral muscular dystrophy	When onset <20 years	With infantile onset	With infantile onset	Slow	Severe infantile onset type is frequently associated with sensorineural deafness

Congenital muscular dystrophy

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
Congenital muscular dystrophy					
All types	Any age depending on severity	Any age depending on severity	Any age depending on severity	Slow	
Ullrich	70% in adolescence	Mild	Infrequent		Proximal contractures with marked distal laxity

Congenital myopathies

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
Congenital myopathy					
Central core	Uncommon except in severe recessive type	Uncommon	Uncommon	Slow	Susceptible to malignant hyperthermia
Minicore	Early while ambulation preserved				
Nemaline	Early in severe neonatal form, mild later onset form may develop early while ambulation preserved	In severe form	In severe form	Slow	
Myotubular	85% in severe X-linked form	In severe form	In severe form	Slow	Ophthalmoplegia, rare coagulopathy and liver haemorrhage

CMS/MM/
CMT/
Pompe's

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
Congenital myasthenic syndromes	Often in neonatal period, may occur during inter-current illnesses	Especially during inter-current illnesses	Possible if weakness severe and persistent		Weakness may fluctuate, episodic apnoea in some. Congenital stridor in those with DOK7 mutations
Mitochondrial myopathy	Common	Possible	Possible	Acute deterioration possible	
Charcot–Marie–Tooth	With severe early onset, especially with GDAP1 mutation	With severe early onset	With severe early onset		Stridor, especially with GDAP1 mutation
Pompe	Infantile onset, may be early in later onset while ambulation preserved	Infantile onset	Infantile onset	Infantile rapid, late onset slow	Variable relationship between motor and respiratory progression

Likelihood of respiratory impairment

Varies greatly

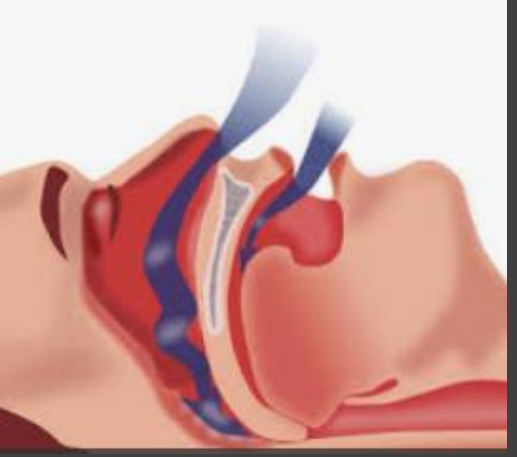
More significant in those with more severe global weakness

Guidelines in respiratory care

There were a number of excellent disease specific guidelines and consensus statements, but none focussed on respiratory management ... Till BTS in 2012

Many principles of respiratory management are not disease specific

Can largely apply to all children with NM weakness



Respiratory complications of neuromuscular weakness

- Gas exchange and pump functions of the respiratory system are compromised
- Difficulty maintaining upper airway muscle tone
- Problems with airway protection
- Reduced efficiency of secretion clearance
- Poor spinal support

Respiratory consequences

Hypoventilation

Upper airway obstruction

Aspiration lung disease

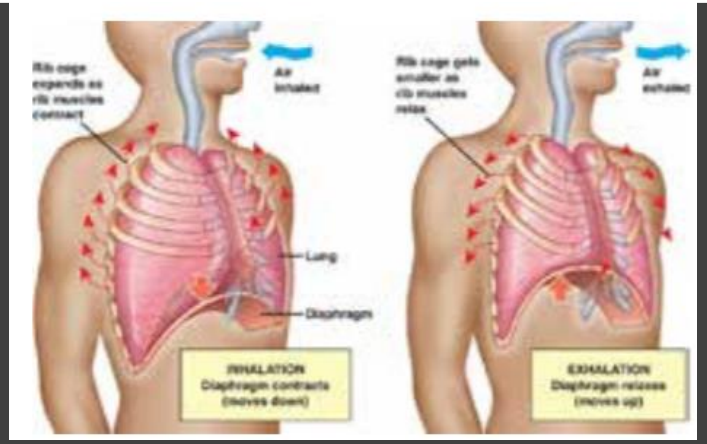
Secretion retention -> Lower airway infection

Mechanical effects of progressive scoliosis

Progressive respiratory insufficiency

Respiratory failure

Death

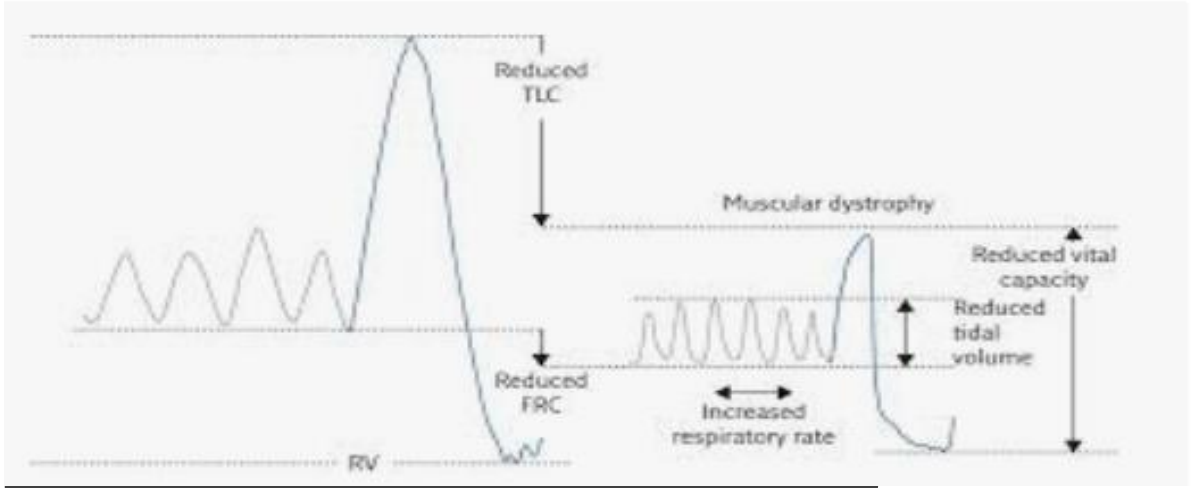


Pulmonary function

Typically a restrictive pattern with reduced vital capacity, total lung capacity and functional residual capacity

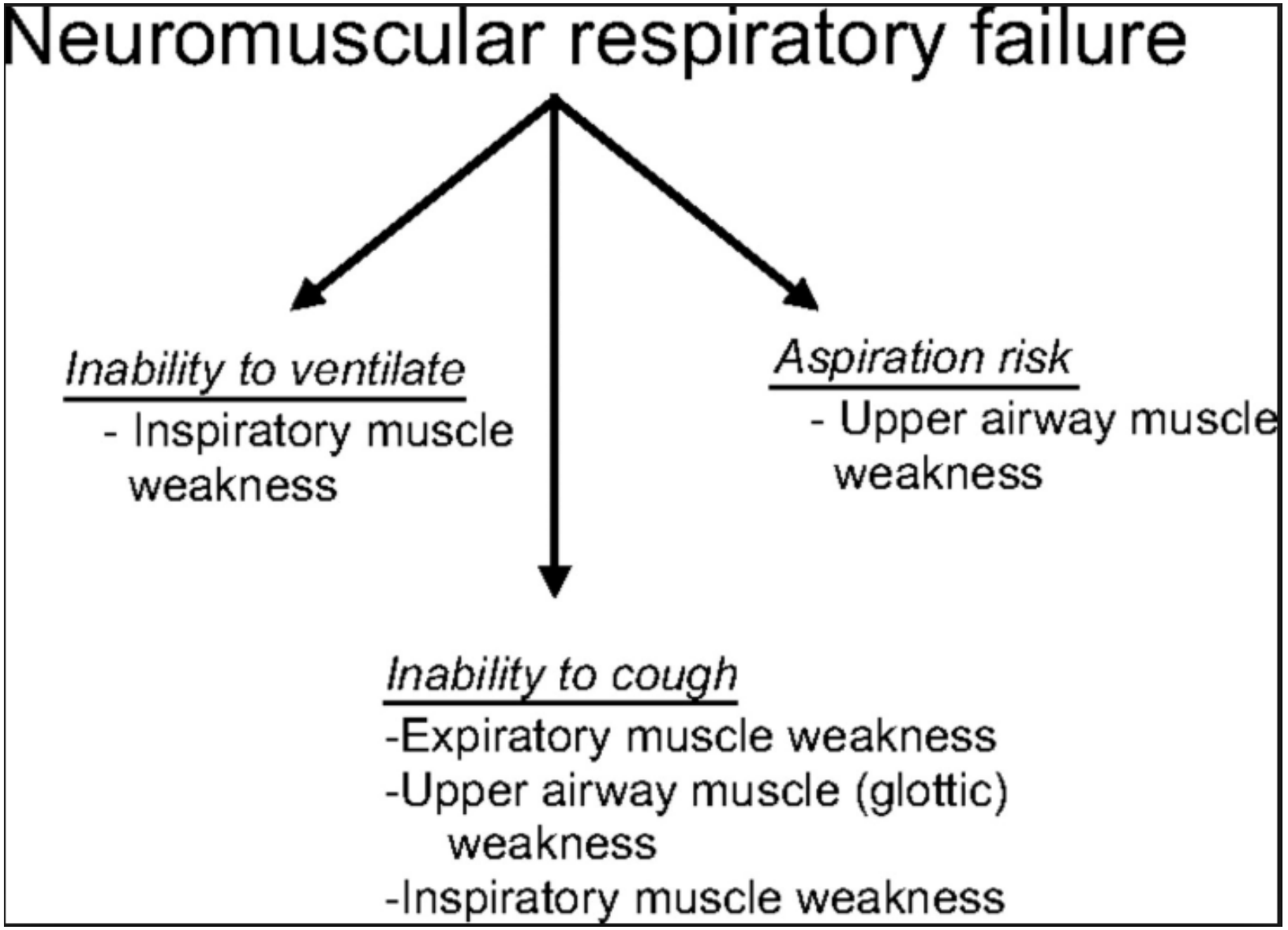
Relative preservation of FEV1/FVC ratio

Scoliosis →worsens the restrictive defect



(Independent of scoliosis)Fibrotic/dystrophic chest wall muscles + shortening of un-stretched tissues → Reduced chest wall compliance

Microatelectasis → reduced lung compliance


Neuromuscular respiratory failure
Inability to ventilate
- Inspiratory muscle weakness
Aspiration risk
- Upper airway muscle weakness
Inability to cough
-Expiratory muscle weakness
-Upper airway muscle (glottic) weakness
-Inspiratory muscle weakness

AAP

Swallowing dysfunction, loss of airway protection & aspiration lung disease

- Parallels progression of muscle weakness
- Difficulties with swallowing -> under nutrition/ risk of aspiration
- Loss of control of larynx and pharynx
- Ineffective cough
- Aspiration of saliva, oral organisms, food, gastric contents
- Airway inflammation, airway obstruction
- Worsening restrictive lung disease, bronchiectasis, pulmonary fibrosis
- Reflux -> a problem in non- mobile children

Retention of airway secretions

Amount of secretions reaching trachea from peripheral airways : 10-100ml/day

Lack of effective coughing:

- Lack of deep inspiration (usually 95% of total lung capacity)
- Poor glottic closure (that requires intact bulbar function)
- Ineffective contraction of the expiratory muscles (abdominal and intercostals)

→unable to generate rapid expiratory flow rates

Respiratory infections, increased airway mucus, impaired ciliary activity

Atelectasis, VQ mismatch, hypoxaemia, reduced lung compliance

Impact of nutritional status

- A challenging problem in children with NM weakness
- At risk of malnutrition (50% of DMD at 14-18 yr old) :
  - Feeding difficulties
  - Dysphagia
  - Reflux
- At risk of obesity
  - 50% of DMD at 13 yr old
- Nasogastric/gastrostomy feeding to maintain adequate nutrition

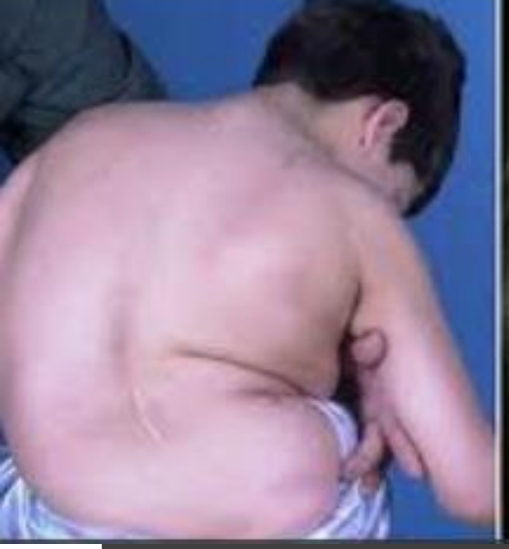
Willig TN, Carlier L, Legrand M, *et al*. Nutritional assessment in Duchenne muscular dystrophy. *Dev Med Child Neurol* 1993;**35**:1074–82.
Sproule DM, Montes J, Dunaway S, *et al*. Adiposity is increased among high-functioning, non-ambulatory patients with spinal muscular atrophy. *Neuromuscular Disord* 2010;**20**:448–52.

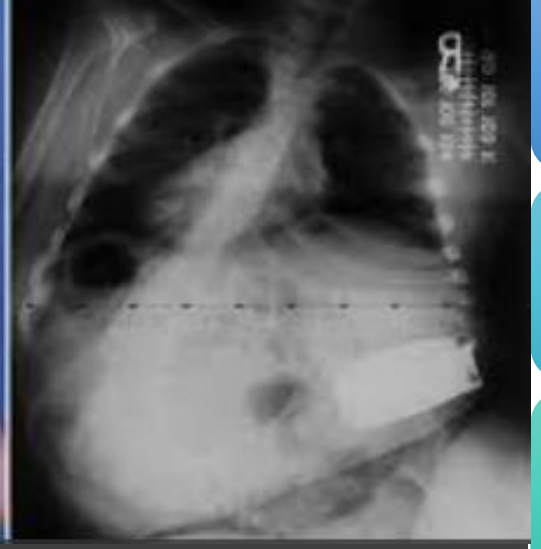
Impact of nutritional status (cont'd)

- Challenges in assessing nutrition:
  - Reduced muscle mass
  - Scoliosis
  - Contractures
- Immobility → **osteoporosis** ← steroids in DMD

- More data needed on : how nutrition impacts lung function

Leroy-Willig A, Willig TN, Henry-Feugeas MC, *et al*. Body composition determined with MR in patients with Duchenne muscular dystrophy, spinal muscular atrophy, and normal subjects. *Magn Reson Imaging* 1997;**15**:737–44.
McDonald CM, Abresch RT, Carter GT, *et al*. Profiles of neuromuscular diseases. Duchenne muscular dystrophy. *Am J Phys Med Rehabil* 1995;**74**(5 Suppl):S70–92.
Goldstein M, Meyer S, Freund HR. Effects of overfeeding in children with muscle dystrophies. *JPEN J Parenteral Enteral Nutr* 1989;**13**:603–7.





Impact of scoliosis

A common feature in many NM conditions

70-90 % of DMD boys & all of SMA 1&2 → significant scoliosis

Lateral curvature of spine → directly displaces thoracic cage & diaphragm , limiting vital capacity by causing asymmetric inspiration & decreased chest wall compliance

Increased physiological dead space, decreased tidal volume to dead space ration

Risk of CO_2 retention

Progression in teenage years→ accelerated growth , increasing weakness, increased sitting time

Light weight orthotic aids, standing frames, well supported wheelchairs

Sleep disordered breathing & hypoventilation

- In normal individuals: reduced ventilatory drive in sleep, reduced upper airway & intercostal muscles tone

Table 4 Sleep disorders associated with common neuromuscular diseases (adapted from Dhand and Dhand 2006)[29]

Disorder	Sleep abnormality
Duchenne muscular dystrophy	Obstructive sleep apnoea (younger patients)
	Hypoventilation (older patients)
Spinal muscular atrophy	Hypoventilation
	Apnoea/hypopnea
Myotonic dystrophy	Hypoventilation
	Apnoea /hypopnea
	Periodic limb movements
	Excessive daytime sleepiness
Peripheral neuropathies (eg, Charcot–Marie–Tooth disease)	Hypoventilation
	Frequent arousals

Episodic hypoventilation during REM with recovery during NREM

Throughout sleep with progressive hypercapnia

- BTS guidelines 2012

Respiratory aims

Reduce this

Most common reason for unplanned hospitalisation: acute respiratory failure from acute respiratory infections

Most common reason of death: chronic respiratory failure

Lengthen lifespan

Box 1 Precipitating factors of acute respiratory failure in children with neuromuscular disease (adapted from Racca *et al*[41])

Upper respiratory tract infections
Pneumonia
Atelectasis
Cardiac failure secondary to cardiomyopathy and/or arrhythmia
Sedative drugs
Aspiration
Pneumothorax
Pulmonary embolism
Acute gastric distension associated with use of non-invasive ventilation

BTS 2012

Racca F, Del Sorbo L, Mongini T, *et al*. Respiratory management of acute respiratory failure in neuromuscular diseases. *Minerva Anestesiol* 2010;**76**:51–62.

Tools to identify children at risk

Clinical assessment

Ulnar length/armspan to replace height measurement

Vital capacity to be measured in all who can perform spirometry

Cough peak flow to assess effective secretion clearance in those > 12 years old

Airway clearance & respiratory muscle training

Augmented cough techniques for those with ineffective cough (>12 yrs old with cough peak flow < 270litres/min

Manual cough assist & air-stacking methods to achieve maximum insufflation capacity

Mechanical insufflation/exsufflation for very weak children

- those with poor bulbar function
- Those who cannot cooperate with manual cough assist or air stacking

Oscillatory techniques

Airway clearance & respiratory muscle training (cont'd)

Nebulised normal saline can be used for tenacious secretions

Consider humidification for those on NIV and with tenacious secretions

Appropriate emergency equipment on hand when using sputum mobilising equipment

Airway clearance & respiratory muscle training (cont'd)

- Use of NIV during airway clearance to prevent respiratory muscle fatigue
- Rest periods during treatment sessions
- Complete treatment session with an insufflation for adequate FRC

Assisted ventilation

NIV support for those with symptomatic nocturnal hypoventilation or daytime hypercapnia

Non invasive approach for those needing daytime ventilation

Pressure –targeted machines work well generally

Modes with fixed Ti appropriate for young/ very weak children

Mouth piece ventilation for older teens during day time

Danger of full face masks

Assisted ventilation

Regular sleep studies to assess those on NIV

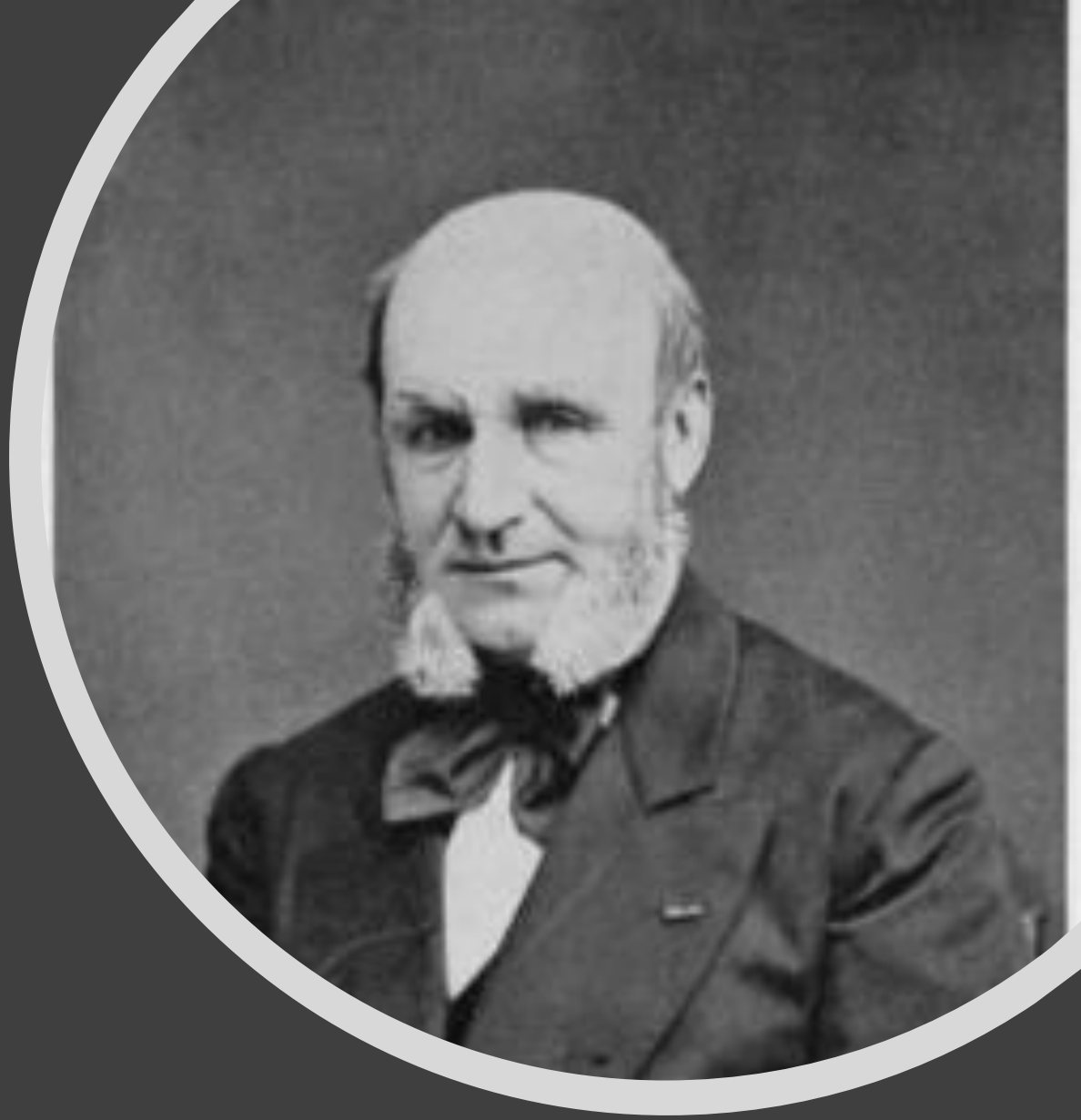
Monitor for complications of NIV /interface

Tracheostomy suitability & care

Oxygen alone not encouraged

Duchenne muscular dystrophy

- First described by French neurologist Guillaume Benjamin Amand Duchenne in the 1860s
- In 1986, researchers identified the gene on the X-chromosome
- In 1987, the protein associated with this gene was identified and named ‘dystrophin’
- Progressive muscle degeneration and weakness
- 1 of 9 types of muscular dystrophy
- X-linked recessive
- Onset at 3-5 yrs old, primarily affects boys
- Exciting research on-going : disease modifying drugs



The DMD patient:

- **DMD patients of varying ages form a large percentage of patients in NM clinic*

- initial screening is recommended before child becomes wheelchair bound

- respiratory assessments step up once patient is non- ambulatory

Birnkrant et al.

Patient Status	Measurements to be Taken During Each Clinic Visit	Frequency
Ambulatory and age 6 years or older	Sitting forced vital capacity (FVC)	At least annually
Non-Ambulatory	Oxyhemoglobin saturation by pulse oximetry Sitting FVC Peak cough flow Maximum inspiratory and expiratory pressures	At least every 6 months
Non-Ambulatory and *any of the following:* • Suspected hypoventilation • FVC < 50% predicted • Current use of assisted ventilation	Awake end-tidal carbon dioxide ($ETCO_2$) level by capnography* *Also measure $ETCO_2$ any time patient with FVC < 50% predicted has a respiratory infection	At least annually

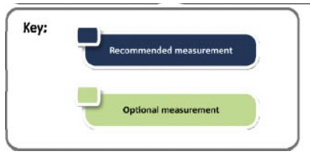


Fig. 1. Respiratory assessment of a patient who has DMD (in the clinic) (adapted from Bushby et al.[2,3]).

The DMD patient:

- respiratory/sleep assessment

-FVC
-Oximetry/PSG
-blood gas

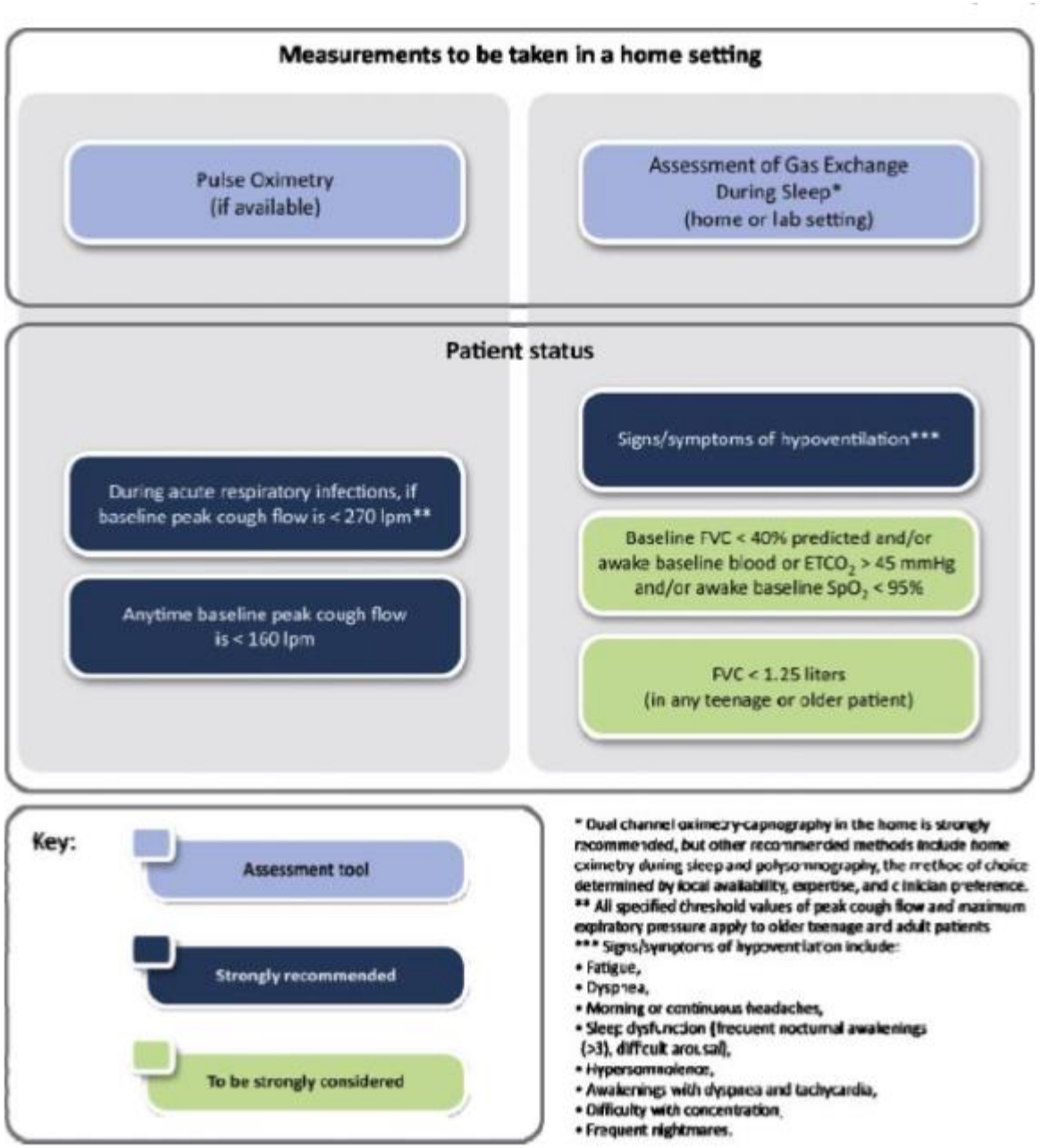


Fig. 2. Respiratory assessment of a patient who has DMD (in the home) (adapted from Bushby et al.[2,3]).

Table 5 Indications for overnight sleep monitoring in children with neuromuscular weakness

Indication	Notes
Vital capacity <60% predicted	Children generally need to be over 6 years of age to produce reliable spirometry. In boys with DMD, a vital capacity of over 1.8 litres indicates that nocturnal hypoventilation is very unlikely to be present
Loss of ambulation because of progressive weakness, or children who never attain the ability to walk	Inability to walk is a measure of moderate to severe muscle weakness
Infants with weakness	Infantile onset is often associated with more severe weakness
Children with symptoms of obstructive sleep apnoea or hypoventilation	See section on clinical assessment
Children with diaphragmatic weakness	Sleep-associated hypoventilation can occur even if general muscle strength is preserved
Children with rigid spine syndrome	These children are at particular risk of nocturnal hypoventilation despite relatively preservation of general muscle strength, ambulation and near normal vital capacity

BTS 2012

The DMD patient:

- regular physiotherapy is recommended
-some patients see Rehab in KKH; some get physio in school/home by AWWA therapists
-LVR (**KKH rehab planning to start*)
-Cough Assist *(rental machines available at MDAS; if for purchase- refer physio/MSW/+/- Homecare)*
-NIV

Birnkrant et al.

Step 1: Volume Recruitment / Deep Lung Inflation Technique

- Volume recruitment / deep lung inflation technique (by self-inflating manual ventilation bag or mechanical in-/ex-sufflation) when FVC < 40% predicted

Step 2: Manual and Mechanically Assisted Cough Techniques

Necessary when:
- Respiratory infection present and baseline peak cough flow < 270 lpm*
- Baseline peak cough flow < 160 lpm or max expiratory pressure < 40cm water
- Baseline FVC < 40% predicted OR < 1.25 liters in older teen / adult

* All specified threshold values of peak cough flow and maximum expiratory pressure apply to older teenage and adult patients

Step 3: Nocturnal Ventilation

Nocturnal ventilation** is indicated in patients who have any of the following:
- Signs or symptoms of hypoventilation (patients with FVC < 30% predicted are at especially high risk)
- A baseline SpO_2 < 95% and/or blood or end-tidal pCO_2 > 45 mmHg while awake
- An apnoea-hyponoea index > 10/hour on polysomnography OR four or more episodes of SpO_2 < 92% OR drops in SpO_2 of at least 4% per hour of sleep

Note: Optimally, use of lung volume recruitment and assisted cough techniques should always precede initiation of non-invasive ventilation.

**Recommended for nocturnal use: non-invasive ventilation with pressure cycled bi-level devices or volume cycled ventilators or combination volume-pressure ventilators.
In bi-level or pressure support modes of ventilation, add a back-up rate of breathing. Recommended interfaces include: a nasal mask or a nasal pillow. Other interfaces can be used and each has its own potential benefits.

The DMD patient:
- intervention

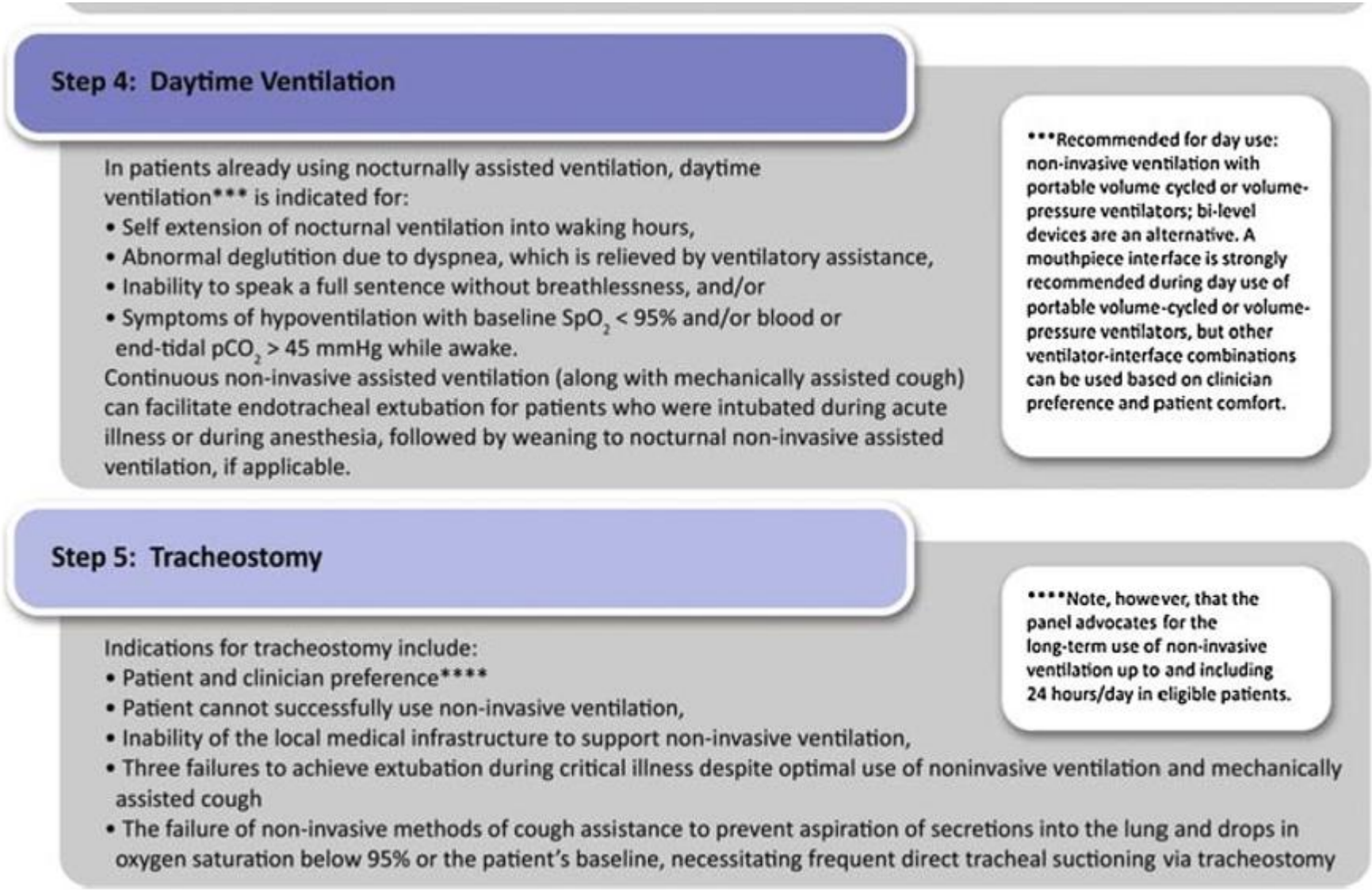
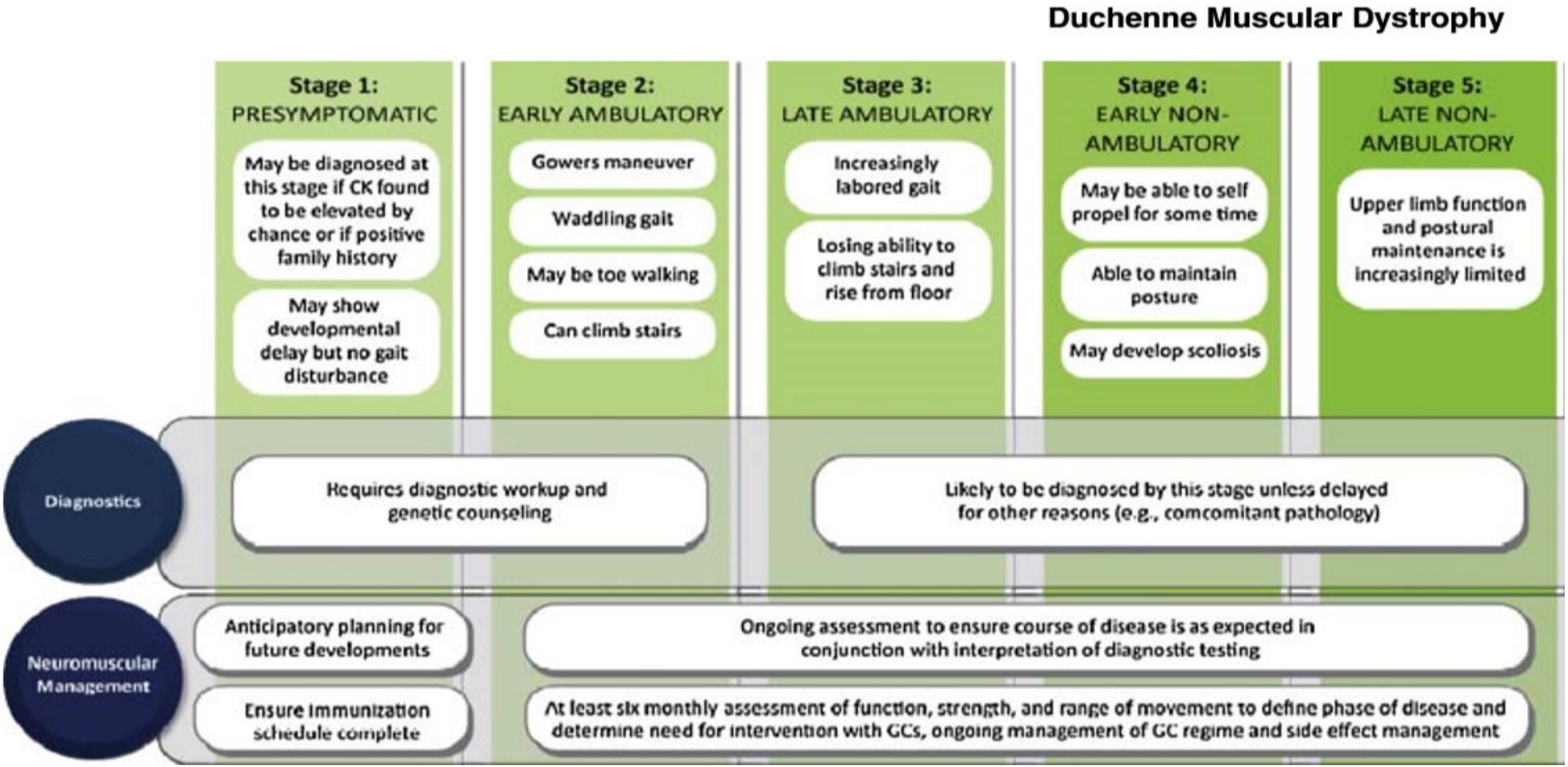
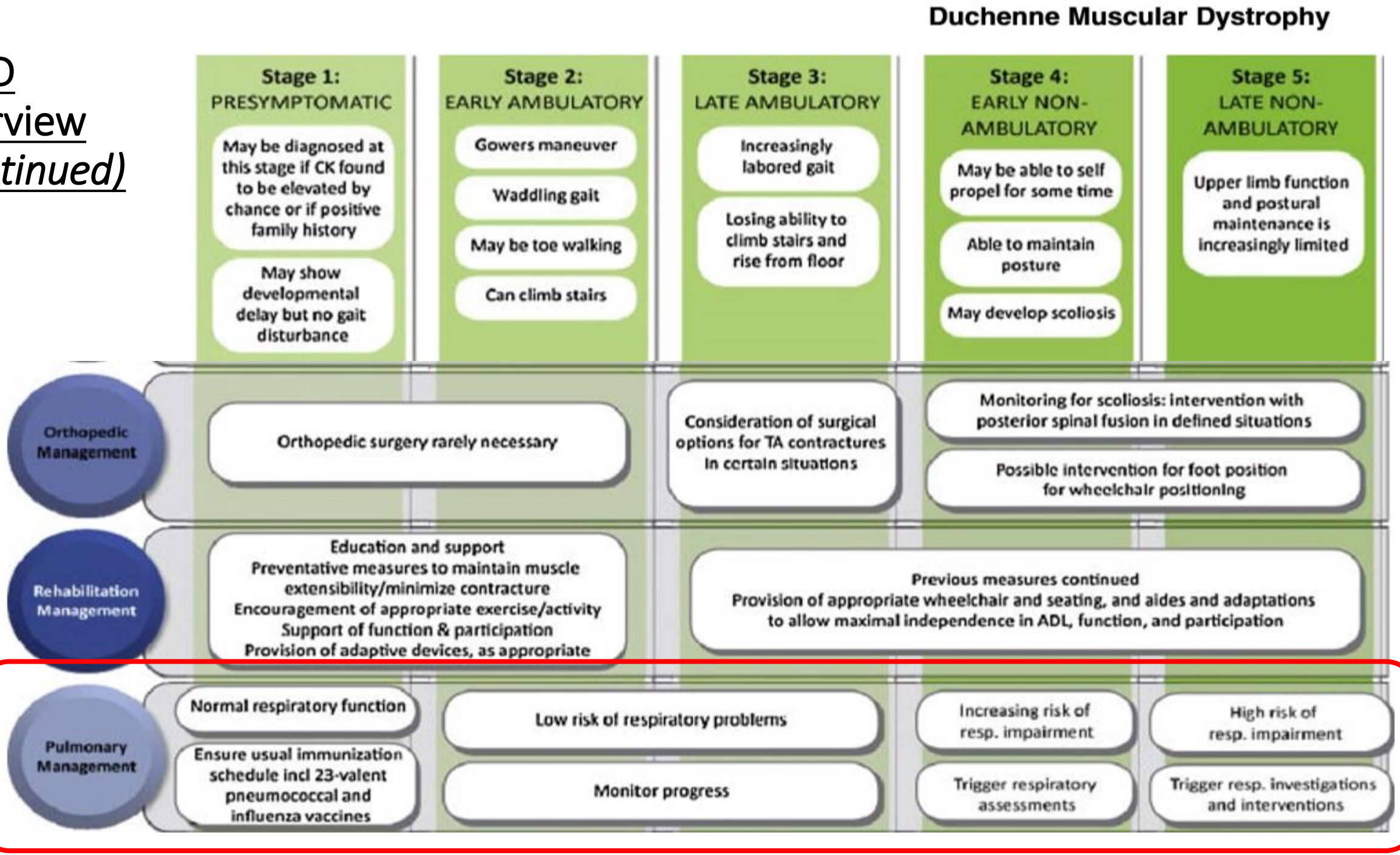


Fig. 3. Respiratory interventions indicated in a patient who has DMD (adapted from Bushby et al.[2,3]).

DMD overview



DMD overview *(continued)*



DMD overview *(continued)*

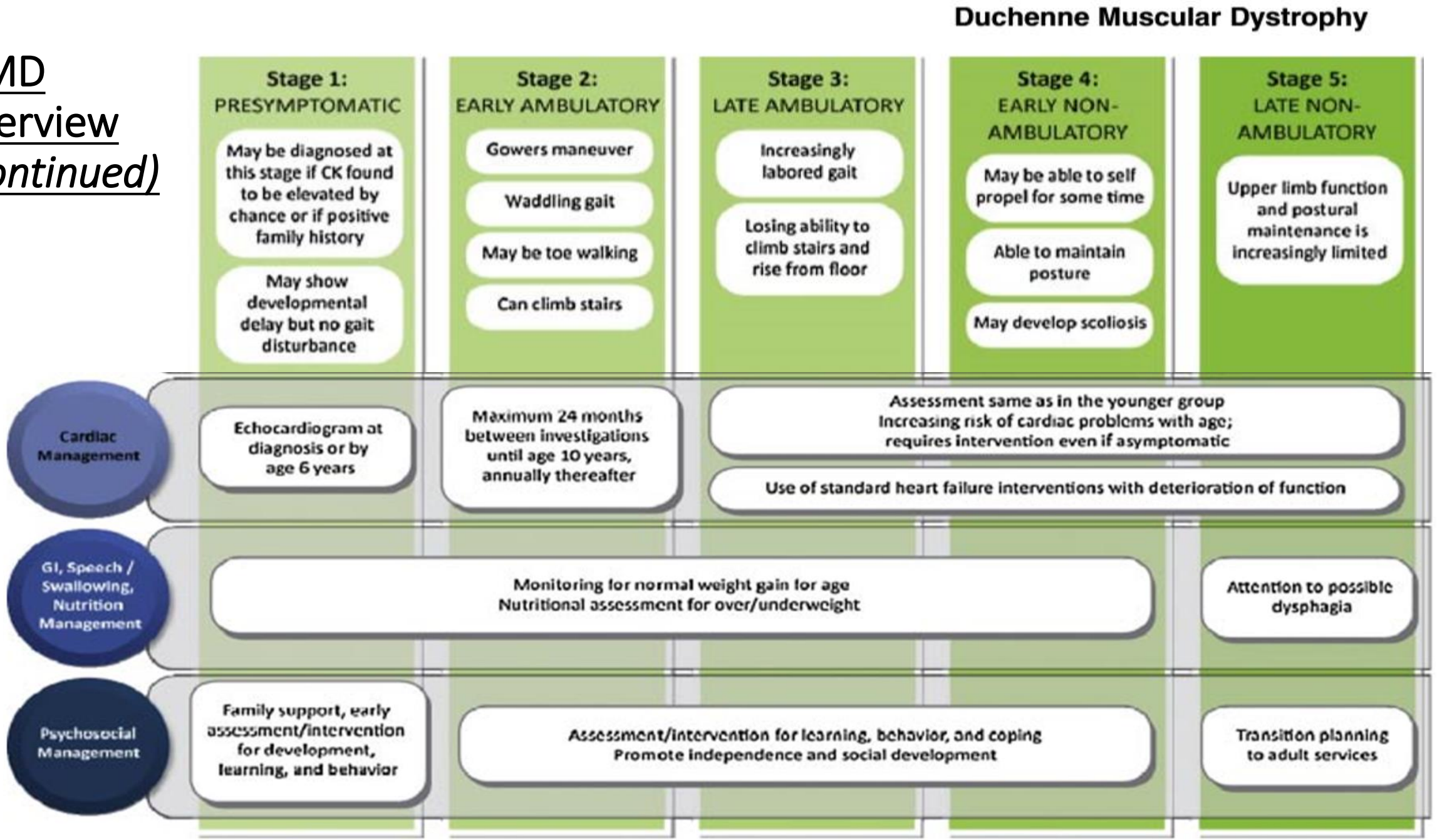


Fig. 4. DMD stages of disease and care considerations (adapted from Bushby et al.[2,3]).

Vaccinations in NM patients *:*

- annual flu vaccine
- pneumococcal vaccines (Prevnar 13; PPSV23)

Table 3
Vaccination recommendations for patients with neuromuscular diseases (NMDs).

Patients	Recommendations
NMD patients with normal immunity who are not taking immunosuppressive therapy	All vaccinations recommended for healthy subjects according to national schedules
NMD patients who are immunocompromised, including those who are taking immunosuppressive therapy	Inactivated vaccines recommended for healthy subjects according to national schedules
	Annual inactivated influenza vaccination
	One dose of pneumococcal vaccination (13-valent pneumococcal conjugate vaccine [PCV13] in addition to primary infant/child series and two doses of 23-valent polysaccharide pneumococcal vaccine [PPSV23]) 5 years or more apart
	Measles, mumps, rubella (MMR) vaccine (with one dose in patients already vaccinated once or two doses in those unvaccinated) at least one month before initiating immunosuppressive therapy
	Varicella vaccine (possibly with two doses) for those who have yet to initiate immunosuppressive therapy and have no evidence of varicella immunity
	Zoster vaccine at least one month before initiating immunosuppressive therapy
	General contraindication to live attenuated vaccines during immunosuppressive therapy and until 3 months after
	Vaccination (including annual influenza vaccination) of household contacts

S. Esposito et al. / Vaccine 32 (2014) 5893–5900

Management of a child with NM weakness

- Multidisciplinary care
- Every child is different !
- Empowering patients and their families
- Transitioning to adult care
- End of life issues


THANK YOU